Ziprasidone mesylate (Geodon for injection): the first injectable atypical antipsychotic medication

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Symptoms of schizophrenia are usually categorized as positive (including delusions, hallucinations, conceptual disorganization, agitation, and paranoia) or negative (including blunted affect, emotional and social withdrawal, apathy, and anhedonia). The worldwide prevalence of this disease is estimated at 1% (1). Traditionally, antipsychotic medications such as chlorpromazine and haloperidol have been used for the treatment of schizophrenia. These agents block dopamine type 2 (D_2) receptors. The major limitations of these agents are their propensity to induce extrapyramidal adverse effects at therapeutic doses and the fact that, in about 30% of patients, the disease is refractory to treatment with these agents or responds inadequately. In addition, these agents have limited efficacy against the negative symptoms of schizophrenia. More recently, novel or "atypical" antipsychotics such as clozapine, olanzapine, risperidone, and quetiapine have become available. These drugs have a tendency to produce fewer extrapyramidal side effects while treating more of the negative symptoms of schizophrenia. These effects are hypothesized to be the result of these drugs' higher affinity for the serotonin $5HT_{2A}$ receptors than for the dopamine D_2 receptors (1).

Haloperidol has been available in both short-acting and long-acting (or depot) injectable forms for decades. Long-acting compounds are administered in the maintenance phase of the treatment of schizophrenia and related psychiatric disorders. Ziprasidone is the first atypical antipsychotic available as an intramuscular injection. The Food and Drug Administration approved the intramuscular formulation of ziprasidone on June 21, 2002 (2).

INDICATION

Intramuscular ziprasidone is indicated for the treatment of acute agitation in schizophrenic patients for whom treatment with ziprasidone is appropriate and who need intramuscular antipsychotic medication for rapid control of agitation (3).

PHARMACOLOGY/PHARMACOKINETICS

Ziprasidone functions as an antagonist at the dopamine D_2 and serotonin $5HT_{2A}$ and $5HT_{1D}$ receptors and as an agonist at the $5HT_{1A}$ receptor. Ziprasidone has the ability to inhibit the synaptic reuptake of serotonin and norepinephrine. The mechanism of action of ziprasidone in the treatment of schizophrenia is unknown, but possible mechanisms may be mediated through a combination of D_2 and $5HT_2$ antagonism (3).

The bioavailability of intramuscular ziprasidone is 100%. Peak serum concentrations usually occur approximately 60 minutes after the dose is administered. The mean half-life ranges from 2 to 5 hours. Little accumulation is observed following 3 days of intramuscular dosing (3).

CLINICAL EFFICACY

Three studies have been published on the use of intramuscular ziprasidone (4–6). All of these studies were performed in the same patient population—patients with acute psychosis related to schizophrenia, schizoaffective disorder, bipolar disorder, schizophreniform disorder, delusional disorder, brief psychotic disorder, or psychotic disorders not otherwise specified as defined by the *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*. The fact that patients were required to give written informed consent for each of these trials precluded enrollment of very hostile, confused, or disorganized patients. The instruments used to measure outcomes in these studies are summarized in *Table 1* (7–11).

Intramuscular ziprasidone 2 mg vs 10 mg

This randomized, double-blind, multicenter trial was designed to compare 2 dosages of intramuscular ziprasidone (2 mg and 10 mg) in the treatment of patients with psychosis and acute agitation for up to 24 hours. A total of 117 patients were randomized to receive an initial ziprasidone dose of either 2 mg (n = 54) or 10 mg (n = 63) followed by up to 3 identical additional doses at intervals of at least 2 hours until the end of the 24-hour study period (maximum of 4 doses in the 24-hour period). The endpoint of each patient's involvement in the study was defined as either 6 hours after administration of the last dose or the end of the 24-hour treatment period, whichever was later, or the time of early termination. The safety and efficacy of intramuscular ziprasidone were evaluated by using the following instruments: Behavioral Activity Rating Scale (BARS) (responders were defined *a priori* as having a ≥2-point reduction in BARS score); Clinical Global Impressions, severity of illness (CGI-S) and global improvement (CGI-I) scales; Positive and Negative Syndrome Scale (PANSS); Barnes Akathisia Scale (BAS); and Simpson-Angus Scale (SAS) (4).

The ziprasidone 10-mg group had a significantly lower mean BARS score than the 2-mg group 15 minutes after the first injec-

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Table 1. Instruments used to measure outcomes in ziprasidone intramuscular clinical trials*

Instrument	Scale	Use
BARS: Behavioral Activity Rating Scale	1 to 7 (difficult or unable to rouse to violent, requires restraint)	Assess level of activity of patients with acute agitation associated with psychosis
BAS: Barnes Akathisia Scale	0 to 5 (absent to severe akathisia)	Assess presence and severity of drug-induced akathisia (inability to remain in a sitting posture)
BPRS: Brief Psychiatric Rating Scale	1 to 7 (not present to extremely severe)	Rate patient behavior and symptoms
CGI: Clinical Global Impressions	Severity of illness (CGI-S): 1 to 7 (normal to extremely ill); global improvement (CGI-I): 1 to 7 (much improved to very much worse); efficacy index: 1 to 4 (none to outweighs therapeutic effect)	Assess treatment response in psychiatric patients
PANSS: Positive and Negative Syndrome Scale	30 items rated on scale of 1 to 7 (absent to extreme)	Evaluate presence/absence and severity of positive, negative, and general psychopathology of schizophrenia (developed from BPRS and psychopathology rating scale)
SAS: Simpson-Angus Scale	10 items, focus on rigidity	Evaluate presence and severity of parkinsonian/extrapyramidal symptomatology

*From references 7–11.

tion ($P < 0.05$). The mean BARS scores continued to decrease in the 10-mg group until 2 hours after the first dose. These scores were significantly lower in the 10-mg group than in the 2-mg group at 3 and 4 hours after administration ($P < 0.01$). No significant differences were noted in the PANSS total scores, the mean PANSS agitation items scores, the CGI-S scores, or the CGI-I scores (4).

Treatment-emergent adverse events were reported in 35.2% of patients in the 2-mg group and 42.9% of patients in the 10-mg group. Headache and pain at the injection site were the only adverse events that were reported in more than 10% of patients in either group. Headache was reported in 5.6% of the 2-mg group and 12.7% of the 10-mg group. Pain at the injection site was reported in 13% of the 2-mg group and 7.9% of the 10-mg group. One patient in the 10-mg group experienced moderate akathisia, and one patient in the 2-mg group experienced mild extrapyramidal symptoms. Agitation was reported in 2 patients in the 2-mg group and in 1 patient in the 10-mg group. Mean reductions in the SAS and BAS scores were reported in both groups. (Statistical analyses were not performed on tolerability and safety assessments in this study.) There was no evidence of clinically significant changes in electrocardiographic variables (4). It is unclear whether enough patients were studied to show a true difference between the 2 dosages.

Intramuscular ziprasidone 2 mg vs 20 mg

This randomized, double-blind, multicenter trial was designed to compare intramuscular ziprasidone 2 mg and 20 mg in a 24-hour study of patients with acute agitation and psychosis. It was identical in design to the 2 mg vs 10 mg study already described. A total of 79 patients were randomized to receive an initial ziprasidone dose of either 2 mg (n = 38) or 20 mg (n = 41), followed by up to 3 identical doses at intervals of at least 4 hours until the end of the 24-hour study (a maximum dosage of 80 mg/day). The endpoint of the patient's involvement in the study was defined as being either 6 hours after administration of the last dose of intramuscular ziprasidone or the end of the 24-hour period, whichever was later. The efficacy and safety of intramuscular ziprasidone were evaluated by using the following instruments: BARS, PANSS, CGI-S, CGI-I, SAS, and BAS (5).

Fifteen minutes after the first intramuscular injection of 20-mg ziprasidone, improvement in the mean BARS score was observed. This effect was significant at 30 minutes (compared with the 2-mg group [$P < 0.01$]) and maximal at 2 hours after the initial injection. At the 2-hour mark, 90.2% of patients in the 20-mg group had a ≥2-point reduction in BARS score, while only 34.2% of the patients in the 2-mg group had a similar reduction ($P < 0.001$). The 20-mg group also displayed significantly greater reductions in mean CGI-S score, mean CGI-I score, and mean PANSS agitation items score than the 2-mg group 4 hours after injection. Except for the PANSS total score, these differences remained statistically significant at the endpoint (5).

Treatment-emergent adverse events were reported in 36.8% of the 2-mg group and 43.9% of the 20-mg group. The most frequently reported event was somnolence, which appeared to be dose related (13.2% of the 2-mg group and 19.5% of the 20-mg group, respectively). Other common adverse events were nausea, injection site pain, and dizziness. Relatively few patients had any increase in either SAS or BAS score at the last observation (10.5% and 13.2%, respectively, for the 2-mg group and 9.8% and 4.9%, respectively, in the 20-mg group). There were no reports of movement disorders, including extrapyramidal symptoms, dystonia, and hypertonia. The maximum QTc interval reported was 475 milliseconds. However, it is important to note that the patients included in this study did not have any clinically significant cardiovascular disease at baseline (5).

This study showed that intramuscular ziprasidone 20 mg is effective in rapidly and significantly reducing the symptoms of acute agitation in patients with psychotic disorders and that it is well tolerated. Enough patients were enrolled to identify a clinically significant treatment difference between the 2 groups. The maximum allowable daily dosage in this study (80 mg/day) is higher than the package insert recommendation of 40 mg/day.

Intramuscular ziprasidone vs intramuscular haloperidol

This randomized, open-label, multicenter, international study was designed to compare intramuscular ziprasidone with intramuscular haloperidol in the treatment of hospitalized psychiatric patients with acute agitation and psychosis. A total of 132 patients were assigned in a 2:1 ratio to receive either ziprasidone (n = 90) or haloperidol (n = 42). Two thirds of patients had been administered antipsychotics in the 48 hours before screening. The total duration of the study was 7 days. Patients received intramuscular treatment for up to 3 days, followed by twice-daily oral therapy until day 7. Those patients in the ziprasidone group received an initial intramuscular dose of 10 mg and, depending on clinical need, subsequent intramuscular doses of 5 to 20 mg every 4 to 6 hours (maximum dosage of 80 mg in 24 hours) for up to 3 days. Oral ziprasidone was then started at a total daily dosage that was either twice the last daily intramuscular dose or 80 mg, whichever was higher. These patients received ziprasidone 80 to 200 mg/day, depending on clinical response, until day 7. Patients in the haloperidol group received an initial intramuscular dose of 2.5 to 10 mg, with subsequent doses administered as needed every 4 to 6 hours (maximum dosage of 40 mg in 24 hours) for up to 3 days. Oral haloperidol was then started at a daily dose that was either equivalent to the total last daily intramuscular dose or 10 mg/day, whichever was higher. These patients received haloperidol 10 to 80 mg/day until day 7. Efficacy assessments included the Brief Psychiatric Rating Scale (BPRS, total and agitation items only) and the CGI. The SAS and the BAS were used to evaluate the presence and severity of parkinsonian symptoms and the presence and severity of drug-induced akathisia, respectively (6).

At the last assessment while the patients were still receiving intramuscular therapy, mean reductions from baseline in BPRS total, BPRS agitation items, and CGI scores were significantly greater in patients who received ziprasidone than in those who received haloperidol. At the endpoint assessment, only the mean reduction from baseline in CGI scores was significantly greater in patients who received ziprasidone than in those who received haloperidol; the mean reduction from baseline for all variables, however, was greater in patients who received ziprasidone (6).

Fewer patients withdrew from the ziprasidone group than from the haloperidol group (8.9% vs 19%). Also, fewer patients in the ziprasidone group than in the haloperidol group experienced any adverse event. This difference was more pronounced during the intramuscular treatment period than during the combined intramuscular and oral treatment period. No patient discontinued intramuscular treatment because of treatment-related adverse events. Twenty-one percent of patients who received intramuscular haloperidol experienced extrapyramidal symptoms, while none of the patients in the ziprasidone group experienced such symptoms. Tremor, dystonia, and hypertonia were also more common in the haloperidol group (2.4%, 7.1%, and 7.1%, respectively) than in the ziprasidone group (1.1%, 1.1%, and 0%, respectively). Akathisia was more common in the ziprasidone group (2.2% vs none in the haloperidol group). By the study's endpoint, all incidences of adverse events were greater in the haloperidol group. Small decreases from baseline in mean SAS and BAS scores were observed with ziprasidone both at the end of intramuscular treatment and at endpoint, while increases in mean SAS and BAS scores were associated with intramuscular haloperidol, with further increases observed at endpoint. Forty-eight percent of haloperidol-treated patients and 14.4% of ziprasidone-treated patients received anticholinergic medication at some time during the study. Electrocardiographic changes from baseline were unremarkable in both groups. No patients had an increase in QTc interval of ≥20% or had a QTc interval >500 milliseconds during either intramuscular or oral treatment with ziprasidone or haloperidol (6).

The authors of this study concluded that the results suggest that intramuscular ziprasidone is significantly more effective than haloperidol in reducing the symptoms of acute psychosis, including agitation, and has well-defined advantages in tolerability over intramuscular haloperidol. Furthermore, they concluded that patients could make the transition from the intramuscular to the oral formulation of ziprasidone with further reduction in symptoms and no increase in burden of adverse effects (6).

The maximum allowable daily dosage of ziprasidone in this study (80 mg/day) exceeds the current package insert recommendation of 40 mg/day. There was no report of a power calculation; therefore, it is unclear whether enough patients were studied to show a true difference between the 2 therapies.

Table 2. Percentage of patients reporting adverse events (≥3% incidence) in studies of short-term fixed-dose intramuscular ziprasidone*

	Dose		
Adverse event	2 mg (n = 92)	10 mg (n = 63)	20 mg (n = 41)
Somnolence	8	8	20
Nausea	4	8	12
Dyspepsia	1	3	2
Dizziness	3	3	10
Insomnia	3	0	0
Diarrhea	3	3	0
Postural hypotension	0	0	5
Headache	3	13	5
Injection site pain	9	8	7
Vomiting	0	3	0

*From reference 3.

ADVERSE EFFECTS

A summary of the most common adverse events reported in patients treated with intramuscular ziprasidone is presented in *Table 2* (3).

CONTRAINDICATIONS/WARNINGS

Ziprasidone is contraindicated in patients with a known history of QT prolongation (including congenital long QT syndrome), with recent acute myocardial infarction, or with uncompensated heart failure (3).

The common cutoff point for concern about ventricular arrhythmias such as torsade de pointes is a QTc value >500 milliseconds. As of February 2000, a QTc interval of ≥500 milliseconds had been reported for 2 of 3095 (0.06%) ziprasidone-treated patients and for 1 of 440 (0.23%) patients taking placebo (12). In addition, none of the 10 reported cases of ziprasidone overdose has been associated with a serious cardiac event or death (13). However, electrocardiographic recordings were obtained in only 2 of the 10 overdoses (14). So far, there have been no reports of torsade de pointes (13). The risk of torsade de pointes and sudden death has become apparent several years after licensing of other noncardiac drugs that cause QTc prolongation (13). Both torsade de pointes and sudden death are rare complications. In addition, most of the clinical trials performed with ziprasidone to date have excluded patients with any history of cardiac disease. Therefore, for all of these reasons, the full clinical impact of the capacity of ziprasidone to prolong the QTc interval has not yet been determined.

Table 3. Cost comparison of intramuscular ziprasidone and intramuscular haloperidol for the treatment of agitated patients with underlying psychosis*

			Mean dose and cost/day		
Drug	Initial dose	Cost	Day 1	Day 2	Day 3
Ziprasidone	10 mg	$17.10	23.3 mg/day ($39.83)	27.6 mg/day ($47.18)	27.6 mg/day ($47.18)
Haloperidol	2.5–10 mg	$0.63–$5.30	7.6 mg/day ($4.03)	10.1 mg/day ($5.35)	11 mg/day ($5.83)

*Costs are based on Baylor University Medical Center acquisition costs. Doses are based on the regimens described in reference 6.

DOSING AND ADMINISTRATION

Intramuscular ziprasidone is available in a single-dose vial as ziprasidone mesylate (20 mg ziprasidone/mL). Ziprasidone should be given at a dose of 10 to 20 mg as required, up to a maximum of 40 mg per day. A total of 10 mg may be administered every 2 hours; doses of 20 mg may be administered every 4 hours up to a maximum of 40 mg/day. The use of intramuscular ziprasidone for more than 3 consecutive days has not been studied. Dosing in elderly patients or in patients with hepatic or renal impairment has not been studied. However, since the cyclodextrin excipient is cleared renally, intramuscular ziprasidone should be administered cautiously in patients with impaired renal function. The coadministration of oral and intramuscular ziprasidone has not been studied and is therefore not recommended.

Ziprasidone is a pregnancy category C agent. There are no well-controlled studies of ziprasidone in pregnant women. Ziprasidone should be used in pregnant women only if the potential benefits outweigh the potential risks. It is not known whether ziprasidone or its metabolites are excreted in human milk. Therefore, it is recommended that women receiving ziprasidone should not breastfeed.

DRUG INTERACTIONS

Ziprasidone has drug interactions that are pharmacodynamic (related to combined pharmacologic effects) and pharmacokinetic (related to alteration in plasma levels). QT interval–prolonging agents, centrally acting agents, antihypertensive agents, and levodopa and dopamine agonists produce pharmacodynamic interactions. Ziprasidone should not be used with any drug that prolongs the QT interval. The effect of ziprasidone may be potentiated when given with other agents that act on the central nervous system. Ziprasidone may enhance the effects of some antihypertensive agents. It may antagonize the effects of levodopa and dopamine agonists. Carbamazepine and ketoconazole produce pharmacokinetic interactions. Carbamazepine decreases the area under the curve of ziprasidone by approximately 35% because carbamazepine is an inducer of CYP3A4. Ketoconazole, an inhibitor of CYP3A4, increases the area under the curve and the maximum clearance of ziprasidone by about 35% to 40%. Cimetidine and antacids do not interact with ziprasidone (3).

Due to the potential additive effect of ziprasidone and other drugs that prolong the QT interval, ziprasidone should not be given with dofetilide, sotalol, quinidine, class IA or class III antiarrhythmics, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol, or tacrolimus. Clinicians should be alert to the identification of other drugs that have been consistently observed to prolong the QTc interval. Certain circumstances may increase the risk of torsade de pointes and sudden death in association with the use of drugs that prolong the QTc interval. These circumstances include bradycardia, hypokalemia or hypomagnesemia, concomitant use of other drugs that prolong the QTc interval, and congenital prolongation of the QT interval. Baseline serum potassium and magnesium measurements are recommended for patients who are at risk of significant electrolyte disturbances. Also, periodic monitoring of serum electrolytes is essential for patients in whom diuretic therapy is introduced during ziprasidone treatment (3).

ECONOMIC ISSUES

A cost comparison of intramuscular ziprasidone and intramuscular haloperidol is summarized in *Table 3*. Dosing is based on the regimen from the study that compared these 2 agents (6). Since the majority of intramuscular ziprasidone use is likely to be in patient populations that have not been studied in clinical trials, a cost comparison of intramuscular ziprasidone and intravenous haloperidol for these populations is included in *Table 4*. According to the regimens compared in Tables 3 and 4, intramuscular ziprasidone is considerably more expensive than injectable haloperidol.

SUMMARY

It is clear from the results of published clinical trials that intramuscular ziprasidone is effective in the treatment of acute agitation in schizophrenic patients. All of the patients studied in these trials had underlying psychosis. It is important to note that the patient populations studied in the clinical trials of intramuscular ziprasidone are different from the patient populations in which this drug is often prescribed.

Many critically ill patients experience delirium as a result of being placed in a stressful environment for prolonged periods of time. This delirium is usually characterized by an acutely changing or fluctuating mental status, inattention, disorganized thinking,

Table 4. Cost comparison of intramuscular ziprasidone and intravenous haloperidol for the treatment of delirium/agitation in critically ill patients*

Drug	Dose	Cost/dose	Cost/day†
Ziprasidone	10–20 mg	$17.10–$34.19	$68.30
Haloperidol	2–10 mg	$1.06–$5.30	$4.24–$21.20

*Costs are based on Baylor University Medical Center acquisition costs.

†Based on a maximum daily ziprasidone dose of 40 mg/day and haloperidol dose of 2 to 10 mg every 6 hours.

and an altered level of consciousness that may or may not be accompanied by agitation. Currently, haloperidol is the preferred agent for the treatment of delirium in critically ill patients. Haloperidol is usually administered intravenously despite a lack of data to define and support this route of administration (15). Extrapolating the results of the published studies on intramuscular ziprasidone to this patient population is difficult given the different routes of administration and the different instruments used to assess safety and efficacy. The instruments used to assess the efficacy of intramuscular ziprasidone in the clinical trials are not the instruments used to assess critically ill patients.

The adverse effect profile of ziprasidone is considerably more benign than that of other antipsychotic agents (such as haloperidol). Extrapyramidal symptoms are common in patients who are taking the older antipsychotic medications. The likely reason for the rare occurrence of extrapyramidal symptoms reported with ziprasidone is the high $5HT_{2A}/D_2$ affinity ratio of ziprasidone. Extrapyramidal symptoms have been associated with D_2 antagonism.

The capacity of ziprasidone to prolong the QTc interval must be considered when selecting an atypical antipsychotic agent. While there have been no reports of fatal events associated with this effect, it cannot be ignored. An additive effect on the QTc interval prolongation may be encountered with the concomitant administration of other drugs that prolong the QTc interval.

Oral ziprasidone is usually initiated at a dosage of 20 mg twice daily. Intramuscular ziprasidone has a greater bioavailability and should be initiated at doses of 10 to 20 mg, up to a maximum of 40 mg per day. The use of intramuscular ziprasidone for more than 3 consecutive days has not been studied.

Intramuscular ziprasidone is considerably more expensive than injectable haloperidol. However, cost is not the only consideration made when evaluating a drug. The decreased incidence of adverse events reported with ziprasidone and the convenience of the availability of both intramuscular and oral formulations must also be considered.

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